Inhaled Corticosteroids and COVID-19

Lipworth, Brian; Kuo, Chris Ruiwen; Lipworth, Samuel; Chan, Rory

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degradation, leading to cardiovascular disease progression in bronchiectasis.

Bronchiectasis is a complex disease, and identification of biomarkers that can assist in risk stratification, targeted interventions, and monitoring strategies are needed, as highlighted by the EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration) research priorities taskforce. In conclusion, we have shown that sDES is a promising biomarker of future mortality and cardiovascular risk in bronchiectasis. This should be validated in future large cohort studies, such as the ongoing European BRIDGE (Bronchiectasis Research Involving Databases, Genomics and Endotyping) study (NCT 03791086) (10). ■

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Jeffrey T.-J. Huang, Ph.D.
Elena Kuzmanova, Ph.D.
Alison J. Dicker, Ph.D.
Holly R. Keir, B.Sc.
Simon Finch, M.D.
University of Dundee
Dundee, United Kingdom

Stefano Aliberti, M.D.
University of Milan
Milan, Italy
and
Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Cá Granda Ospedale Maggiore Policlinico
Milan, Italy

Thomas C. Fardon, M.D.
James D. Chalmers, M.D., Ph.D.*
University of Dundee
Dundee, United Kingdom

*Corresponding author (e-mail: j.chalmers@dundee.ac.uk).

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To the Editor:

Maes and colleagues (1) present data from lung tissue that showed that mRNA expression for ACE2 (angiotensin-converting enzyme 2) was significantly greater in 38 patients with moderate chronic obstructive pulmonary disease (COPD) compared with 61 healthy control subjects but not compared with a group of 7 patients with asthma or asthma–COPD overlap syndrome. Furthermore, values for ACE2 expression in a heterogeneous group of 23 patients with obstructive airway disease (OAD) comprising COPD, asthma–COPD overlap syndrome, or asthma not receiving inhaled corticosteroids (ICS) were significantly higher than values in 56 control subjects but not values in 25 patients with OAD receiving ICS.

The problem with interpreting these results in a heterogeneous group of patients with OAD is that ACE2 is upregulated in smokers and in those with COPD but is downregulated in those with asthma and those with atopy (2, 3). Furthermore, assaying ACE2 mRNA only tells one-half of the story with regard to entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into lung tissue, as asthma and atopy are both associated with upregulation of TMPRSS2 (transmembrane protease serine 2) in airway epithelial cells (3). In this regard, in induced sputum cells from asthma patients, ICS have been shown to exhibit suppressive effects *ex vivo* on both ACE2 and TMPRSS2 expression (4).

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Maes and colleagues (1) fail to point out the inhibitory *in vitro* effects of ICS on local and systemic production of IL-6 (5, 6), this being the strongest predictor for impending respiratory failure in severe coronavirus disease (COVID-19) (7). Finally, a more specific suppressive effect from ICS on SARS-CoV-2 replication has been described with ciclesonide and mometasone furoate but not with budesonide, beclomethasone, or fluticasone (8).

We believe that, taken together, these observations reinforce the need for patients with eosinophilic asthma and COPD to continue receiving their controller therapy containing ICS, as that will provide optimal disease control and perhaps also confer protection against viral triggers, perhaps including SARS-CoV-2. ■

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Brian Lipworth, M.D.*
Chris RuiWen Kuo, M.B. Ch.B.
University of Dundee
Dundee, United Kingdom

Samuel Lipworth, M.B. Ch.B.
University of Oxford
Oxford, United Kingdom

Rory Chan, M.B. Ch.B.
University of Dundee
Dundee, United Kingdom

ORCID ID: 0000-0002-8140-2014 (B.L.).

*Corresponding author (e-mail: b.j.lipworth@dundee.ac.uk).

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Reply to Lipworth *et al.*

From the Editorialists:

We totally agree with the letter by Lipworth and colleagues in response to our editorial emphasizing that patients with asthma need to continue using their inhaled corticosteroid (ICS)-containing controller therapy during the coronavirus disease (COVID-19) pandemic, as this provides optimal asthma control and also confers some protection against viral triggers, perhaps including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). They also highlight several interesting papers, published after the publication of our editorial, which address two key research questions: *1*) are subjects with asthma at increased risk of COVID-19 infection and related illness? and *2*) does ICS use modulate this risk? Because asthma is a very heterogeneous disease, we hypothesize that asthma phenotypes and the type of underlying airway and systemic inflammation need to be taken into account to answer these questions correctly (*see* Table 1).

In children with asthma, allergic sensitization and other type 2 biomarkers (such as fractional exhaled nitric oxide and epithelial expression of IL-13, which increases the expression of inducible nitric oxide synthase) were inversely related to ACE2 (angiotensin-converting enzyme 2), the cellular receptor for SARS-CoV-2 (2). Moreover, in ICS-naive adults with mild allergic asthma, segmental allergen bronchoprovocation significantly reduced ACE2 expression in the bronchial epithelium. In contrast, nonatopic asthma was not associated with reduced ACE2 expression, which is in line with the findings by Peters and colleagues (3), demonstrating no difference in ACE2 gene expression in induced sputum of subjects of the SARP-3 (Severe Asthma Research Program-3) as compared with healthy control subjects, as atopy is less prevalent in adults with severe asthma. In addition, in samples from bronchial brushes and biopsies, there were similar levels of ACE2 mRNA expression in healthy volunteers and adult subjects with mild-to-moderate asthma or

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